Appendices

Appendix 1. Patient-reported adverse drug event questionnaire

Questionnaire
Drug use and side effects experienced by patients

This questionnaire contains questions about the drugs that you take and any side effects (adverse effects) that you experience from these drugs. The questionnaire is made up of two parts:

Part A: general information, your drug use and the symptoms you experience

Part B: side effects that you have experienced during the past four weeks

Your details will remain confidential at all times.

Instructions

Most of the questions can be answered by checking the box next to the most applicable answer. There are no right or wrong answers and there will generally only be one possible answer, unless stated otherwise. There are also a number of questions that ask you to provide additional information on the dotted lines.

If you check the box next to the wrong answer, you can color that box black and then check the box next to the right answer. For example:

Are you married?

■ No

☒ Yes

The intended answer in this example was 'Yes'.

Most respondents take between 20 and 40 minutes to complete the questionnaire. You may need more time or less time to complete it yourself.

Please feel free to take a break during the questionnaire, but we do ask that you complete it at a later time, as incomplete questionnaires cannot be used for this research.

Thank you very much for your cooperation

Part A

General Information

1. What is your gender?
   - ☐ Male
   - ☐ Female

2. How old are you?
   ☐ years

3. What town/city do you live in?
   .....

4. What is your highest level of completed education?
   - ☐ No education completed
   - ☐ Elementary school, special education
   - ☐ Junior secondary vocational education, pre-vocational education (for example VMBO, LTS, LEAO)
   - ☐ Junior general secondary education (for example MAVO, MULO, ULO, VMBO-t)
   - ☐ Senior secondary vocational education, other vocational education (for example MBO, MEAO, MTS, BBL)
   - ☐ Senior general secondary education (for example HAVO, VWO, Athenaeum, HBS)
   - ☐ Higher professional education (for example HBO, HTS, HEAO)
   - ☐ University education (research university)
   - ☐ Other (please specify).....

5. What is your country of birth?
   - ☐ The Netherlands
   - ☐ Other (please specify).....

6. What is your father's country of birth?
   - ☐ The Netherlands
   - ☐ Other (please specify).....
   - ☐ Don't know

7. What is your mother's country of birth?
   - ☐ The Netherlands
   - ☐ Other (please specify).....
   - ☐ Don't know

8. How would you describe your general health?
   - ☐ Excellent
   - ☐ Very good
   - ☐ Good
   - ☐ Fair
   - ☐ Poor

Part A

Drug use

9. Which prescription drugs did you take during the **past 4 weeks**?

Example: I took metformin 500mg for diabetes.	
Example name + strength *metformin 500mg*	**Example** disease/disorder *diabetes*

Please enter all prescription drugs that you took during the past 4 weeks below:

Name + **strength** of the drug	For which **disorder**/**disease** /**ailment** did or do you take this drug?

Question 9. Drug use, continued

Name + strength of the drug	For which **disorder/disease /ailment** did or do you take this drug?

10. Do you suffer from other disorders or diseases besides those mentioned above?
    - ☐ No
    - ☐ Yes (please specify).....

11. Did you use drugs during the past 4 weeks for which you did not require a prescription (for example self-help drugs, incidental drugs or alternative, homeopathic or natural drugs)?
    - ☐ No
    - ☐ Yes (please specify).....

Part A

Symptoms

12. Did you experience symptoms during the **past 4 weeks**?

- If yes, you can find lists of symptoms per body part on the following pages. You should first consider in which part of your body you experienced the symptoms. You can then go to the page mentioned for each of the body parts. There you can check the box next to the applicable symptom.

☐ **Yes**, I experienced symptoms in the following parts of my body:

☐ No, I did not experience any symptoms..... ➔ go to page 26 (in Part B)

Part A

Eyes and/or eyelids

13. Which symptoms involving your 'eyes and/or eyelids' did you experience during the **past 4 weeks** (you may give more than one answer)?

	Yes, I experienced this symptom and ...	
	I **don't** think the drug caused it or I'm not sure ▼	I **do** think that it is, or could be, a **side effect** of my drug ▼
Blurred vision	☐	☐
Double vision	☐	☐
Seeing less or poorer vision	☐	☐
Seeing (black) spots	☐	☐
Night blindness	☐	☐
Flashes of light	☐	☐
Painful eyes	☐	☐
Teary, watery eyes	☐	☐
Dry eyes	☐	☐
Burning, itchy or irritated eyes	☐	☐
Inflamed eyes	☐	☐
Itchy or irritated eyelids	☐	☐
Inflamed eyelids	☐	☐
Puffy or swollen eyes or eyelids	☐	☐
Enlarged pupils	☐	☐
Pressure on the eyes	☐	☐
Burst eye vessels	☐	☐
Inability to move eyes	☐	☐
Unusual eye movements	☐	☐
Other (please specify)	☐	☐

Part A

Throat, nose, ears (hearing) and/or swallowing

14. Which symptoms involving your 'throat, nose, ears (hearing) and/or swallowing' did you experience during the **past 4 weeks** (you may give more than one answer)?

	Yes, I experienced this symptom and ...	
	I **don't** think the drug caused it or I'm not sure ▼	I **do** think that it is, or could be, a **side effect** of my drug ▼
Painful throat, throat-ache	☐	☐
Inflamed throat	☐	☐
Dry throat	☐	☐
Difficulty swallowing, food sticks in the throat	☐	☐
Choking	☐	☐
Changed sense of smell (for example sensitivity to odors)	☐	☐
Bloody nose, nosebleed	☐	☐
Dry nostrils	☐	☐
Blocked nose	☐	☐
Runny nose	☐	☐
Ear infection	☐	☐
Earache	☐	☐
Buzzing or ringing in the ear or ears	☐	☐
Impaired hearing, difficulty hearing or deafness	☐	☐
Other (please specify)	☐	☐

Part A

Sweating, blushing, temperature increase or decrease, colds and/or flu

15. Which symptoms involving 'sweating, blushing, temperature, colds and/or the flu' did you experience during the **past 4 weeks** (you may give more than one answer)?

	Yes, I experienced this symptom and ...	
	I **don't** think the drug caused it or I'm not sure ▼	I **do** think that it is, or could be, a **side effect** of my drug ▼
Shivering, shivery	☐	☐
Goose bumps	☐	☐
Cold limbs (for example cold feet and/or hands)	☐	☐
Often cold	☐	☐
Lower body temperature	☐	☐
Higher body temperature (not fever)	☐	☐
Fever (temperature above 38 degrees Celsius)	☐	☐
Insufficient sweating/transpiration	☐	☐
Excessive sweating/transpiration	☐	☐
Blushing	☐	☐
Cold	☐	☐
Flu-like symptoms	☐	☐
Coughing, barking, hawking	☐	☐
Sneezing	☐	☐
Swollen glands	☐	☐
Other (please specify)	☐	☐

Part A

Mouth, lips, speech and/or voice

16. Which symptoms involving your 'mouth, lips, speech and/or voice' did you experience during the **past 4 weeks** (you may give more than one answer)?

	Yes, I experienced this symptom and ...	
	I **don't** think the drug caused it or I'm not sure	I **do** think that it is, or could be, a **side effect** of my drug
	▼	▼
Ulcers or bumps in the mouth and/or on the roof of the mouth	☐	☐
Increased saliva in the mouth	☐	☐
Dry mouth, less saliva in the mouth	☐	☐
Painful or sensitive mouth	☐	☐
Lockjaw	☐	☐
Bad breath	☐	☐
Inflamed lips	☐	☐
Painful or sensitive lips	☐	☐
Dry lips	☐	☐
Swollen lips	☐	☐
Voice change (for example hoarseness, huskiness)	☐	☐
Unclear speech, mumbling, speech difficulties	☐	☐
Word-finding problems, stumbling speech	☐	☐
Other (please specify)	☐	☐

Part A

Tongue, teeth, gums and/or taste

17. Which symptoms involving your 'tongue, teeth, gums and/or taste did you experience during the **past 4 weeks** (you may give more than one answer)?

	Yes, I experienced this symptom and ...	
	I **don't** think the drug caused it or I'm not sure	I **do** think that it is, or could be, a **side effect** of my drug
	▼	▼
Tooth discoloration	☐	☐
Plaque	☐	☐
Caries, tooth decay	☐	☐
Toothache	☐	☐
Teeth grinding	☐	☐
Inflamed or irritated gums	☐	☐
Bleeding gums	☐	☐
Sensitive gums	☐	☐
Painful or sensitive tongue	☐	☐
Swollen tongue	☐	☐
Tingling tongue	☐	☐
Changed sense of taste	☐	☐
Tongue blistering	☐	☐
Dry tongue	☐	☐
Tongue discoloration	☐	☐
Other (please specify)	☐	☐

Part A

Lungs, heart, chest, breathing (including sleep apnea) and/or blood (blood pressure, bleeding)

18. Which symptoms involving your 'lungs, heart, chest, breathing and/or blood' did you experience during the **past 4 weeks** (you may give more than one answer)?

	Yes, I experienced this symptom and ...	
	I **don't** think the drug caused it or I'm not sure ▼	I **do** think that it is, or could be, a **side effect** of my drug ▼
Hiccups	☐	☐
Lung disorder	☐	☐
Pneumonia	☐	☐
Pneumothorax	☐	☐
Respiratory infection	☐	☐
Hyperventilation	☐	☐
Apnea (gap between breaths longer than 10 seconds)	☐	☐
Sleep apnea (gaps or pauses between breaths while sleeping)	☐	☐
Slow breathing	☐	☐
Rapid breathing	☐	☐
Shortness of breath, wheeziness, difficulty breathing, quickly out of breath	☐	☐
Panting, puffing, wheezing, whistling (heavy breath)	☐	☐
Palpitations	☐	☐
Rapid heartbeat	☐	☐
Slow heartbeat	☐	☐
Irregular heartbeat, arrhythmia	☐	☐
Chest pain or pressure	☐	☐
Blood poisoning	☐	☐
Hemorrhage	☐	☐
High blood pressure	☐	☐
Low blood pressure	☐	☐
Anemia	☐	☐
Thrombosis	☐	☐
Other (please specify)	☐	☐

Page 12.

Part A

Bladder and/or urination

19. Which symptoms involving your 'bladder and/or urination' did you experience during the **past 4 weeks** (you may give more than one answer)?

	Yes, I experienced this symptom and ...	
	I **don't** think the drug caused it or I'm not sure	I **do** think that it is, or could be, a **side effect** of my drug
	▼	▼
Blood in urine	☐	☐
Urine discoloration	☐	☐
Pain when urinating	☐	☐
Burning sensation when urinating	☐	☐
Less frequent and/or difficulty urinating	☐	☐
More frequent need to urinate	☐	☐
Less urine per toilet visit	☐	☐
Urine incontinence (involuntary urine loss)	☐	☐
Pressure on the bladder	☐	☐
Bladder infection	☐	☐
Other (please specify)	☐	☐

Part A

Intestines, stomach, vomiting (including vomiting blood), stool and/or bowel movements

20. Which symptoms involving your 'intestines, stomach, vomiting, feces and/or bowel movements' did you experience during the **past 4 weeks** (you may give more than one answer)?

	Yes, I experienced this symptom and ...	
	I **don't** think the drug caused it or I'm not sure	I **do** think that it is, or could be, a **side effect** of my drug
	▼	▼
(Excessive) burping, belching	☐	☐
Nauseous, sick	☐	☐
Acid indigestion, stomach acid, heartburn	☐	☐
Vomiting reflex	☐	☐
Vomiting	☐	☐
Vomiting blood	☐	☐
Bloated feeling	☐	☐
Bloated stomach	☐	☐
Intestinal, stomach, abdominal cramps and/or pain	☐	☐
Gurgling or rumbling in the intestines and/or stomach	☐	☐
Flatulence (gas)	☐	☐
Hemorrhoids	☐	☐
Fecal incontinence (involuntary loss of feces)	☐	☐
Diarrhea	☐	☐
Runnier, softer feces (not diarrhea)	☐	☐
Mucus in feces	☐	☐
Blood with feces	☐	☐
Blood in feces	☐	☐
Blockage, constipation, hard feces	☐	☐
Black feces	☐	☐
More frequent bowel movements	☐	☐
Other (please specify)	☐	☐

Part A

Skin (including wounds, bruises, rashes), hair and/or nails

21. Which symptoms involving your 'skin, hair and/or nails' did you experience during the **past 4 weeks** (you may give more than one answer)?

	Yes, I experienced this symptom and ...	
	I **don't** think the drug caused it or I'm not sure ▼	I **do** think that it is, or could be, a **side effect** of my drug ▼
Greasy skin	☐	☐
Warm/burning skin	☐	☐
Dry, rough skin	☐	☐
Painful skin	☐	☐
Itchiness	☐	☐
Flaking	☐	☐
Acne	☐	☐
Blisters	☐	☐
Rashes (for example red patches, pimples)	☐	☐
Spot (painful), ulcer, wound	☐	☐
Skin discoloration (for example yellow or pale skin)	☐	☐
Pigment stains	☐	☐
Patches of little or no skin pigment (pale patches of skin)	☐	☐
Bruises, contusions	☐	☐
Increased sensitivity of the skin to light	☐	☐
Weak hair	☐	☐
Loss of hair	☐	☐
Increased hair growth	☐	☐
Nail discoloration	☐	☐
Wrinkled nails	☐	☐
Brittle, fragile nails	☐	☐
Other (please specify)	☐	☐

Part A

Genitals, sexuality, menopause, breasts and/or menstruation

22. Which symptoms involving your 'genitals, sexuality, menopause, breasts and/or menstruation' did you experience **during the past 4 weeks** (you may give more than one answer)?

	Yes, I experienced this symptom and ...	
	I **don't** think the drug caused it or I'm not sure	I **do** think that it is, or could be, a **side effect** of my drug
	▼	▼
Vaginal discharge	☐	☐
Vaginal bleeding	☐	☐
Vaginal dryness (insufficient moisture production in the vagina)	☐	☐
Burning sensation in the vagina	☐	☐
Irritated vagina	☐	☐
Menstruation pain	☐	☐
Irregular menstruation	☐	☐
Heavy menstruation (excessive loss of blood or excessively long menstruation)	☐	☐
Absence of menstruation	☐	☐
Painful breasts or breast	☐	☐
Prostate complaints	☐	☐
Sperm discoloration	☐	☐
Erection problems, impotence	☐	☐
Painful erection	☐	☐
Painful penis	☐	☐
Irritated penis	☐	☐
Testicle pain	☐	☐
Breast growth (in men)	☐	☐
Pain during and/or after intercourse	☐	☐
Reduced sexual desire/interest in sex	☐	☐
Increased sexual desire/interest in sex	☐	☐
Difficulty having an orgasm	☐	☐
No orgasm	☐	☐
Painful orgasm	☐	☐
Hot flushes	☐	☐
Premature menopause	☐	☐
Other (please specify)	☐	☐

Page 16.

Part A

Muscles, bones, joints and/or bodily complaints

23. Which symptoms involving your 'muscles, bones, joints and/or bodily complaints' did you experience during the **past 4 weeks** (you may give more than one answer)?

	Yes, I experienced this symptom and ...	
	I **don't** think the drug caused it or I'm not sure	I **do** think that it is, or could be, a **side effect** of my drug
	▼	▼
Muscle cramps (for example leg cramp)	☐	☐
Muscle pain, susceptible to muscle ache	☐	☐
Muscle contractions	☐	☐
Weak muscles, decreased muscular strength	☐	☐
Tired, heavy muscles	☐	☐
Stiff muscles, stiffness (for example stiff neck)	☐	☐
Muscle tension	☐	☐
Quivering, trembling, shaking muscles	☐	☐
Restless legs	☐	☐
Bone fracture or fractures	☐	☐
Bone pain	☐	☐
Painful joints	☐	☐
Inflammatory arthritis (gout)	☐	☐
Stiff joints	☐	☐
Unusual and/or involuntary movements or twitches	☐	☐
Difficulty walking	☐	☐
No or numb sensation in	☐	☐
Tingling or prickling sensation in	☐	☐
Pain in	☐	☐
Bruised or damaged muscle, bone, body part	☐	☐
Other (please specify)	☐	☐

Part A

Dizziness, falling and/or balance

24. Which symptoms involving 'dizziness, falling and/or balance' did you experience during the **past 4 weeks** (you may give more than one answer)?

	Yes, I experienced this symptom and ...	
	I **don't** think the drug caused it or I'm not sure	I **do** think that it is, or could be, a **side effect** of my drug
	▼	▼
Unsteadiness, insecure, unsteady feeling	☐	☐
Balance problems	☐	☐
Falling	☐	☐
Fainting	☐	☐
Light-headedness	☐	☐
Dizziness	☐	☐
Poorer coordination	☐	☐
Other (please specify)	☐	☐

Part A

Head, brain, moods and/or emotions

25. Which symptoms involving your 'head, brain, moods and/or emotions' did you experience during the **past 4 weeks** (you may give more than one answer)?

	Yes, I experienced this symptom and ...	
	I **don't** think the drug caused it or I'm not sure	I **do** think that it is, or could be, a **side effect** of my drug
	▼	▼
Stroke	☐	☐
Headache	☐	☐
Migraine	☐	☐
High, drunken sensation	☐	☐
Impaired consciousness	☐	☐
Lack of concentration	☐	☐
Lower reaction time	☐	☐
Memory loss	☐	☐
Forgetfulness	☐	☐
Black-out	☐	☐
Confusion	☐	☐
Over-sensitive, irritable	☐	☐
Restless	☐	☐
Aggressive	☐	☐
Nervous, tense	☐	☐
Anxious, fretful, worried	☐	☐
Absent-minded	☐	☐
Disorientated	☐	☐
Lack of emotions	☐	☐
Over-emotional	☐	☐
Depressed, somber	☐	☐
Crying fits	☐	☐
Changed mood	☐	☐
Mood swings	☐	☐
Changed personality	☐	☐
Voices in the head	☐	☐
Hallucinations	☐	☐
Psychosis	☐	☐
Other (please specify)	☐	☐

Part A

Sleep, dreams, fatigue, yawning and/or more or less energy

26. Which symptoms involving 'sleep, dreams, tiredness, yawning and/or energy' did you experience during the **past 4 weeks** (you may give more than one answer)?

	Yes, I experienced this symptom and ...	
	I **don't** think the drug caused it or I'm not sure	I **do** think that it is, or could be, a **side effect** of my drug
	▼	▼
Sleep attacks	☐	☐
Sleep problems, sleeplessness	☐	☐
Sleepiness, dullness, heavy eyelids	☐	☐
Dreams, nightmares	☐	☐
Fatigue	☐	☐
Yawning	☐	☐
More energetic	☐	☐
Listlessness, dullness, lethargy, lack of energy	☐	☐
Other (please specify)	☐	☐

Part A

Eating, drinking, weight and/or blood sugar

27. Which symptoms involving 'eating, drinking, weight and/or blood sugar did you experience during the **past 4 weeks** (you may give more than one answer)?

	Yes, I experienced this symptom and ...	
	I **don't** think the drug caused it or I'm not sure	I **do** think that it is, or could be, a **side effect** of my drug
	▼	▼
Decreased appetite	☐	☐
Increased appetite	☐	☐
Excessive thirst	☐	☐
Sensitive to alcohol (less able or unable to handle alcohol)	☐	☐
Increased weight	☐	☐
Loss of weight	☐	☐
Low blood sugar level (hypoglycemia)	☐	☐
High blood sugar level (hyperglycemia)	☐	☐
Unstable blood sugar level	☐	☐
Other (please specify)	☐	☐

Page 20.

Part A

Inflammation, edema, fungal infection and/or all other complaints

28. Which symptoms involving 'infection, fungus infection edema and/or all other complaints' did you experience during the **past 4 weeks** (you may give more than one answer)?

	Yes, I experienced this symptom and ...	
	I **don't** think the drug caused it or I'm not sure	I **do** think that it is, or could be, a **side effect** of my drug
	▼	▼
Fungal infection ----------	☐ ----------	☐ ----------
Edema, bloating ----------	☐ ----------	☐ ----------
Inflammation of	☐ ----------	☐ ----------
Other symptoms:		
.....	☐ ----------	☐ ----------
.....	☐ ----------	☐ ----------
.....	☐ ----------	☐ ----------
.....	☐ ----------	☐ ----------
.....	☐ ----------	☐ ----------

Part B. Questions per side effect

In Part A of the questionnaire you were asked which symptoms you experienced in the past 4 weeks. In each case you indicated whether you thought it could be a side effect of your drugs.

In Part B you are asked to provide more information about these possible side effects. Please answer the questions 29 to 43 for **each side effect**.

In other words, you answer the questions on the **first side effect** on pages 23 to 25, the questions on the **second side effect** on the next three pages, etc.

Feel free to refer to Part A to see which side effects you checked.

Did you not experience any side effects of your drugs during the **past 4 weeks**?
➔ Please go to **page 26**

Part B

Side effect 1.

29. Can you describe the side effect in your own words?
.....
.....
.....

30. When did you **first** experience this side effect of your drugs?
- ☐ Today
- ☐ Yesterday
- ☐ 2-7 days ago
- ☐ Between 1 week and 1 month ago
- ☐ Between 1 and 6 months ago
- ☐ Between 6 and 12 months ago
- ☐ More than 12 months ago

31. Has this side effect gone away by now or improved?
- ☐ No, the side effect has not gone away yet
- ☐ No, but the side effect has clearly improved
- ☐ No, but the side effect was treated and has now improved
- ☐ Yes, the side effect:
  - ☐ went away by itself
  - ☐ went away after I stopped taking the drug
  - ☐ went away after treatment
  - ☐ other (please specify).....

32. How often did you experience this side effect during the past 4 weeks (on how many or which days)?
.....

33. On the days that you experienced this side effect, how much did it bother you (how bad or intense was it)?
- ☐ Not at all
- ☐ Only a bit
- ☐ Somewhat
- ☐ Quite a lot
- ☐ Very much

34. On the days that you experienced this side effect, how much influence did it have on your daily functioning?
- ☐ None
- ☐ Only a bit
- ☐ Somewhat
- ☐ Quite a lot
- ☐ Very much

35. Did this side effect result in serious medical situations for yourself during the past 4 weeks?
- ☐ No
- ☐ Yes, please specify (you may select more than one answer):
  - ☐ Admitted to hospital
  - ☐ Permanent incapacity to work
  - ☐ Life-threatening situation
  - ☐ Other (please specify) ....

Part B

36. What action did you take in relation to this side effect during the past 4 weeks?
    - ☐ Nothing
    - ☐ In consultation with a healthcare professional, the drug dosage was reduced
    - ☐ I reduced the dosage of the drug by myself
    - ☐ In consultation with a healthcare professional, I stopped taking the drug temporarily
    - ☐ I stopped taking the drug temporarily by myself
    - ☐ In consultation with a healthcare professional, I stopped taking the drug permanently
    - ☐ I stopped taking the drug by myself
    - ☐ A drug and/or remedy has been prescribed to reduce/relieve the side effect, please specify.....
    - ☐ I started using other drugs and/or remedy by myself to reduce/relieve the side effect, please specify .....
    - ☐ Other, please specify.....

37. Why do you think this symptom was caused by your drug (you may give more than one answer)?
    - ☐ I did not experience this symptom before I started taking the drug
    - ☐ The symptom started soon after I started taking the drug
    - ☐ I experienced this symptom less often before I started taking the drug
    - ☐ The symptom was less serious before I started taking the drug
    - ☐ The symptom went away when I stopped taking the drug and came back when I started taking it again
    - ☐ The symptom went away when I stopped taking the drug
    - ☐ The symptom started or grew worse when the drug dosage was increased
    - ☐ The symptom decreased or went away when the drug dosage was decreased
    - ☐ A healthcare professional (for example a doctor or pharmacist) confirmed this
    - ☐ The symptom is described in the patient leaflet
    - ☐ Other (please specify).....

38. Which drug or drugs do you think caused this side effect?
    - ☐ One drug that I use (please specify):.....
    - ☐ More than one drug that I use (please specify):
      .....
    - ☐ I don't know → please go to **question 42**

39. How sure are you that this side effect is caused by this drug or these drugs?
    - ☐ Very sure
    - ☐ Quite sure
    - ☐ Not very sure
    - ☐ Very unsure

40. How long had you been using this drug or these drugs before this side effect started occurring?
    .....

Part B

41. How satisfied are you with the drug (or drugs) described in question 38 when you consider both **this particular** side effect and the effect of the drug or drugs?
    - ☐ Very satisfied
    - ☐ Satisfied
    - ☐ Neither satisfied or dissatisfied
    - ☐ Dissatisfied
    - ☐ Very dissatisfied

42. Do you think there are other reasons for your experiencing this side effect (other than your drugs)?
    - ☐ No
    - ☐ Yes (please specify):

      .....

43. Have you experienced this side effect in the past in combination with **other drugs**?
    - ☐ No
    - ☐ Yes (please specify which drug):

Part B

Please note!

Have you completed Part B for all the side effects you experienced in the last 4 weeks?

Are there not enough forms to complete the questions? Please ask the researcher for more copies.

This is the end of the questionnaire. Please check whether you have answered all the questions.

You may make any further remarks below:

.....

.....

.....

.....

.....

Once again, thank you very much for your cooperation

Appendix 2. Supplemental tables chapter 1

Supplemental table 1. 2x2 tables for test-retest reliability at Patient level, MedDRA® level and ADE specific level

			T2		Total
Patient level			No ADE	≥1 ADE	
	T1	No ADE	28	5	33
		≥1 ADE	4	8	12
	Total		32	13	45
MedDRA level			No ADE in MedDRA	≥1 ADE in MedDRA	
	T1	No ADE in MedDRA	764	13	777
		≥1 ADE in MedDRA	16	17	33
	Total		780	30	810
ADE specific level			ADE not reported	ADE reported	
	T1	ADE not reported	11247	29	11276
		ADE reported	42	22	64
	Total		11289	51	11340

T1 = First measurement; T2 = Second measurement after one week period

Supplemental table 2. 2x2 tables for reliability of body categories at patient level, MedDRA® level and ADE specific level

			T2		Total
Patient level			No ADE	≥1 ADE	
Group with body categories at T1	T1	No ADE	31	3	34
		≥1 ADE	3	8	11
	Total		34	11	45
Group with body categories at T2	T1	No ADE	28	6	34
		≥1 ADE	4	7	11
	Total		32	13	45
MedDRA level			No ADE in MedDRA	≥1 ADE in MedDRA	
Group with body categories at T1	T1	No ADE in MedDRA	768	18	786
		≥1 ADE in MedDRA	13	11	24
	Total		781	29	810
Group with body categories at T2	T1	No ADE in MedDRA	747	23	770
		≥1 ADE in MedDRA	29	11	40
	Total		776	34	810
ADE specific level			ADE not reported	ADE reported	
Group with body categories at T1	T1	ADE not reported	11280	25	11305
		ADE reported	26	9	35
	Total		11306	34	11340
Group with body categories at T2	T1	ADE not reported	11216	50	11266
		ADE reported	63	11	74
	Total		11279	61	11340

T1 = First measurement; T2 = Second measurement after one week period

Supplemental table 3. 2x2 tables and kappa values for test-retest reliability at patient level, MedDRA® level and ADE specific level (only patients who completed second questionnaire within 10 days)

			T2		Total	Kappa value (95% CI)
Patient level			No ADE	≥1 ADE		0.510 (0.16-0.86)
	T1	No ADE	21	5	26	
		≥1 ADE	1	5	6	
	Total		22	10	32	
MedDRA level			No ADE in MedDRA	≥1 ADE in MedDRA		0.453 (0.19-0.72)
	T1	No ADE in MedDRA	553	10	563	
		≥1 ADE in MedDRA	6	7	13	
	Total		559	17	576	
ADE specific level			ADE not reported	ADE reported		0.300 (0.07-0.52)
	T1	ADE not reported	8019	22	8041	
		ADE reported	15	8	23	
	Total		8034	30	8064	

T1 = First measurement; T2 = Second measurement after one week period. CI = Confidence interval.

Supplemental table 4. 2x2 tables and kappa values for reliability of body categories at patient level, MedDRA® level and ADE specific level (only patients who completed second questionnaire within 10 days)

			T2		Total	Kappa value (95% CI)
Patient level			No ADE	≥1 ADE		
Group with body categories at T1	T1	No ADE	22	3	25	0.633
		≥1 ADE	1	5	6	(0.30-0.97)
	Total		23	8	31	
Group with body categories at T2	T1	No ADE	19	4	23	0.439
		≥1 ADE	2	4	6	(0.04-0.84)
	Total		21	8	29	
MedDRA level			No ADE in MedDRA	≥1 ADE in MedDRA		
Group with body categories at T1	T1	No ADE in MedDRA	532	10	542	0.541
		≥1 ADE in MedDRA	6	10	16	(0.32-0.76)
	Total		538	20	558	
Group with body categories at T2	T1	No ADE in MedDRA	490	16	506	0.335
		≥1 ADE in MedDRA	9	7	16	(0.08-0.59)
	Total		499	23	522	
ADE specific level			ADE not reported	ADE reported		
Group with body categories at T1	T1	ADE not reported	7773	15	7788	0.373
		ADE reported	15	9	24	(0.15-0.60)
	Total		7788	24	7812	
Group with body categories at T2	T1	ADE not reported	7247	35	7282	0.176
		ADE reported	20	6	26	(0.00-0.39)
	Total		7267	41	7308	

T1 = First measurement; T2 = Second measurement after one week period. CI = Confidence interval.

Appendix 3. Supplemental tables chapter 2

Supplemental table 1. Algorithm of the patient-reported causality assessment

Item	Description	Answer	Scores
Causality 1	I did not experience this symptom before I started taking the medication	Yes	1
Causality 2	The symptom started soon after I started taking the medication	Yes	1
Causality 3	I experienced this symptom less often before I started taking the medication	Yes	1
Causality 4	The symptom was less serious before I started taking the medication	Yes	1
Causality 5	The symptom went away when I stopped taking the medication and came back when I started taking it again	Yes	2
Causality 6	The symptom went away when I stopped taking the medication	Yes	1
Causality 7	The symptom started or grew worse when the medication dosage was increased	Yes	1
Causality 8	The symptom decreased or went away when the medication dosage was decreased	Yes	1
Other reasons	Do you think there are other reasons for your experiencing this side effect (other than your medication)?	Yes	-1
Which drug + certainty	No drug reported	I don't know	-1
	One or more drugs reported + Patient's certainty	One drug More than one Very sure Quite sure	1
	One or more drugs reported + Patient's uncertainty	One drug More than one Not very sure Very unsure	0

Supplemental table 2. Characteristics of patients who mentioned ≥1 particular drugs and who mentioned no particular drug for their ADE

	Patients who mentioned ≥1 particular drugs to ≥1 ADEs (N=25)	Patients who did not mention a particular drug to any of their ADEs (N=12)	P-value
Mean age in years (SD)	61 (10)	67 (10)	0.118*
Education (%)			1.000†
Lower education	7 (28)	4 (33)	
Middle education	8 (32)	4 (33)	
Higher education	9 (36)	4 (33)	
Other	1 (4)	0 (0)	
Female (%)	8 (32)	3 (25)	0.663‡

ADE = Adverse drug event; SD = Standard deviation
* T-test; † Fisher-Freeman-Halton test; ‡ χ^2-test

Supplemental table 3. Characteristics of ADEs for which ≥1 particular drugs and no particular drugs were mentioned

	ADEs for which ≥1 particular drug(s) were mentioned (N=78)	ADEs for which no particular drugs were mentioned (N=68)	P-value
First time experiencing the ADE (%)			0.021†
Today	2 (3)	4 (6)	
Yesterday	0 (0)	1 (2)	
2-7 days ago	5 (6)	0 (0)	
Between 1 week and 1 month ago	12 (15)	2 (3)	
Between 1 and 6 months ago	8 (10)	6 (9)	
Between 6 and 12 months ago	10 (13)	11 (16)	
More than 12 months ago	41 (53)	44 (65)	
ADE gone away or improved (%)			0.041†
Not yet	57 (73)	63 (93)	
Clearly improved	11 (14)	3 (4)	
ADE was treated and has improved	3 (4)	1 (2)	
ADE went away by itself	0 (0)	0 (0)	
ADE went away after quitting medication	1 (1)	0 (0)	
ADE went away after treatment	1 (1)	0 (0)	
Other	5 (6)	1 (2)	
How much bothersome (%)			0.239†
Not at all	5 (6)	6 (9)	
Only a bit	9 (12)	13 (19)	
Somewhat	37 (47)	34 (50)	
Quite a lot	18 (23)	13 (19)	
Very much	9 (12)	2 (3)	
Influence daily functioning (%)			0.090†
None	29 (37)	18 (27)	
Only a bit	7 (9)	17 (25)	
Somewhat	31 (40)	23 (34)	
Quite a lot	10 (13)	8 (12)	
Very much	1 (1)	1 (2)	
Causality assessment (%)			
I did not experience this symptom before I started taking the medication	47 (60)	40 (59)	0.860‡
The symptom started soon after I started taking the medication	26 (33)	7 (10)	0.001‡
I experienced this symptom less often before I started taking the medication	4 (5)	13 (19)	0.010†
The symptom was less serious before I started taking the medication	3 (4)	5 (7)	0.473†
The symptom went away when I stopped taking the medication and came back when I started taking it again	2 (3)	0 (0)	0.499†
The symptom went away when I stopped taking the medication	0 (0)	1 (2)	0.466†
The symptom started or grew worse when the medication dosage was increased	9 (12)	0 (0)	0.004†
The symptom decreased or went away when the medication dosage was decreased	1 (1)	0 (0)	1.000†
A healthcare professional confirmed this	18 (23)	4 (6)	0.005†
The symptom is described in the patient leaflet	12 (15)	10 (15)	0.909‡

ADE = Adverse drug event; † Fisher-Freeman-Halton test; ‡ χ^2-test

Supplemental table 4. Patient-reported ADE–drug association and information in Summary of Product Characteristics (SPC)

Medical Dictionary for Regulatory Activities (MedDRA®) terminology of the reported ADE	Name of particular drugs mentioned for the ADE (RVG[e]/EU number[f]; date of the SPC)	ADE in SPC
Clustered ADEs[a]		
Dry throat + Dry mouth + Tongue dry + Thirst	Amitriptyline (RVG 52947-52948; date 09-2010)	Yes
Blurred vision + Vision decreased	Rosuvastatin (RVG 26872; date 09-07-2012)	No
Bloated feeling + Abdominal distension	Macrogol, combination (RVG 100287; date 16-05-2012)	Yes
Dry mouth + Fall + Libido decreased	- Formoterol/budesonide (RVG 25887; date 01-11-2011) - Simvastatin (RVG 25536-25539, 33211; date 18-04-2012) - Metformin (RVG 25368, 21698; date 08-2011) - Acenocoumarol (RVG 04464; date 01-2012)	1x Yes based on description 3x No
Hypoglycaemia + Blood glucose Fluctuation	Quetiapine (RVG 20826-20828, 25602-25603, 25128; date 22-02-2012)	No
Dizziness + Balance Difficulty	Irbesartan (EU/1/97/046/001-003, 010, 013; date 22-04-2009)	Yes
Dysphasia + Dysarthria + Sore Mouth	- Quetiapine (RVG 20826-20828, 25602-25603, 25128; date 22-02-2012) - Valproic acid (RVG 06175-06176, 07419, 08659-08661; date 16-04-2012)	1x Yes 1x No
Gastrointestinal pain + Flatulence	Metformin (RVG 25368, 21698; date 08-2011)	Yes
Diarrhoea + Increased stool frequency	Metformin (RVG 25368, 21698; date 08-2011)	Yes
Myalgia + Muscle stiffness	Atorvastatin (RVG 21081-21083, 27148; date 14-06-2012)	Yes
Vomiting reflex + Gastrointestinal pain	- Metformin (RVG 25368, 21698; date 08-2011) - Tolbutamide (RVG 15523-15524; date 30-10-2012)	2x Yes
Diarrhoea + Faecal incontinence	- Metformin (RVG 25368, 21698; date 08-2011) - Tolbutamide (RVG 15523-15524; date 30-10-2012)	2x Yes
Taste alteration + Decreased appetite	- Metformin (RVG 25368, 21698; date 08-2011) - Tolbutamide (RVG 15523-15524; date 30-10-2012)	1x Yes 1x No
Mycosis + Other classified as itching	Metformin (RVG 25368, 21698; date 08-2011)	No
Listlessness + Insomnia + Fatigue	- Atorvastatin (RVG 21081-21083, 27148; date 14-06-2012) - Rosuvastatin (RVG 26872; date 09-07-2012)	2x Yes
Balance difficulty + Balance disorder	- Quetiapine (RVG 20826-20828, 25602-25603, 25128; date 22-02-2012) - Valproic acid (RVG 06175-06176, 07419, 08659-08661; date 16-04-2012)	2x Yes

Single ADEs		
Hypohidrosis[b,c]	Metformin (RVG 25368, 21698; date 08-2011)	No
Heartburn[b,c,d]	Metformin (RVG 25368, 21698; date 08-2011)	Yes
Hearing impaired[b,c,d]	Hydroquinine)RVG 03166; date 09-03-2009)	Yes
Stools loose[b,c,d]	Metformin (RVG 25368, 21698; date 08-2011)	Yes
Increased appetite[b,c,d]	Pramipexole (RVG 101918-101920; date 05-10-2010)	Yes
Flatulence[b,c,d]	Metformin (RVG 25368, 21698; date 08-2011)	Yes
Black stools[b,c,d]	Ferrous fumarate (RVG 50165; date 10-09-2012)	Yes
Flu like symptoms[b,c]	Rosuvastatin (RVG 26872; date 09-07-2012)	Yes based on description
Other classified as numbness[b,c,d]	Perindopril (RVG 33327-33328; date 12-2010)	Yes
Urine discoloration[b,c]	Vildagliptin (EU/1/07/414/001-010, 018; date 17-09-2009)	Yes based on description
Sore throat[b]	Lisinopril (RVG 28424-6; date 11-2012)	Yes based on description
Diarrhoea[b,c]	Macrogol, combination (RVG 100287; date 16-05-2012)	Yes
Tongue dry[b,c]	Metformin (RVG 25368, 21698; date 08-2011)	No
Abdominal discomfort[b,c]	Macrogol, combination (RVG 100287; date 16-05-2012)	Yes
Hyperhidrosis	- Metformin (RVG 25368, 21698; date 08-2011) - Candesartan (RVG 21704-21706, 30755; date 31-12-2011)	2x No
Tingling tongue[b,c]	Candesartan (RVG 21704-21706, 30755; date 31-12-2011)	No
Increased stool frequency[b,c]	Macrogol, combination (RVG 100287; date 16-05-2012)	Yes
Diarrhoea[b]	Liraglutide (EU/1/09/529/001-005; date 08-07-2009)	Yes
Abdominal discomfort[b]	Liraglutide (EU/1/09/529/001-005; date 08-07-2009)	Yes
Weight decreased[b]	Liraglutide (EU/1/09/529/001-005; date 08-07-2009)	Yes
Hyperglycaemia[b]	Liraglutide (EU/1/09/529/001-005; date 08-07-2009)	No
Flatulence[b]	Liraglutide (EU/1/09/529/001-005; date 08-07-2009)	Yes
Weight increased[b,c]	Insulin aspart (EU/1/00/142/004, 005; date 11-05-2012)	Yes
Other classified as concentration impairment	- Tramadol (RVG 21626; date 28-09-2012) - Amitriptyline (RVG 52947-52948; date 09-2010) - Naproxen (11195-6; 08-2012)	3x Yes
Hair loss	- Tramadol (RVG 21626; date 28-09-2012) - Amitriptyline (RVG 52947-52948; date 09-2010) - Naproxen (11195-6; 08-2012)	1x No 2x Yes
Weight increased	- Glimepiride (RVG 31961-31965; date 21-10-2010) - Simvastatin (RVG 25536-25539, 33211; date 18-04-2012)	2x No
Increased appetite[b,c]	Metformin (RVG 25368, 21698; date 08-2011)	No
Haemorrhage[b,c]	Acetylsalicyclic acid (RVG 16466; date 10-11-2008)http://www.whocc.no/atc_ddd_index/?code=N02BA01&showdescription=yes	Yes

Nausea[b,c]	Methotrexate (RVG 28636-28638; date 03-2012)	Yes
Sleep apnea	- Irbesartan (EU/1/97/046/001-003, 010, 013; date 22-04-2009) - Hydrochlorothiazide (RVG 09640-09641; date 20-03-2012) - Sotalol (RVG 16723-16724; date 24-12-2008)	1x No 2x Yes
Weight increased[b]	Quetiapine (RVG 20826-20828, 25602-25603, 25128; date 22-02-2012)	Yes
Constipation[b,c]	Paracetamol/codeine (RVG 12030; date 31-07-2012)	Yes
Hypertonia[b]	Metformin (RVG 25368, 21698; date 08-2011)	No
Abdominal discomfort[b,c]	Metformin (RVG 25368, 21698; date 08-2011)	No
Depressed mood	- Metformin (RVG 25368, 21698; date 08-2011) - Tolbutamide (RVG 15523-15524; date 30-10-2012)	1x No 1x Yes
Irritability	- Metformin (RVG 25368, 21698; date 08-2011) - Tolbutamide (RVG 15523-15524; date 30-10-2012)	1x No 1x Yes
Hyperglycaemia	- Metformin (RVG 25368, 21698; date 08-2011) - Tolbutamide (RVG 15523-15524; date 30-10-2012)	2x No
Increased stool frequency	- Metformin (RVG 25368, 21698; date 08-2011) - Tolbutamide (RVG 15523-15524; date 30-10-2012)	2x Yes
Tooth discolouration	Metformin (RVG 25368, 21698; date 08-2011) or perindopril (RVG 33327-33328; date 12-2010)	No
Vaginal irritation	Glibenclamide (RVG 56114-56115; date 10-2010) or metformin (RVG 25368, 21698; date 08-2011)	No

ADE = Adverse drug event

[a] Clustered ADEs are multiple related ADEs reported by a patient that were clustered into one overall ADE by the researchers

[b] Single ADE-single drug = included in patient-reported causality assessment

[c] Single ADE-single drug associations with a causality score higher than or equal to the median

[d] Single ADE-single drug associations with a causality score higher than or equal to the third quartile

[e] RVG number: Drug registration has been conducted in the Netherlands

[f] EU number: Drug registration is for the whole European Union

Appendix 4. Supplemental tables chapter 3

Supplemental table 1. Sensitivity analyses of the validity of reporting adverse drug events at MedDRA® primary class level in the questionnaire with a recall period of 4 weeks and 3 months

	TP	FP	TN	FN	Se (95% CI)	PPV (95% CI)
Excluding delayed diary completers[a]						
4-week recall; last 4 weeks of diary (N=30*18)	2	16	518	4	33% (4-78)	11% (1-35)
3-month recall; full 3-month diary (N=31*18)	16	16	491	35	32% (19-46)	50% (32-68)
Excluding delayed questionnaire completers[b]						
4-week recall; last 4 weeks of diary (N=37*18)	2	19	641	4	33% (4-78)	10% (1-30)
3-month recall; full 3-month diary (N=34*18)	17	16	548	31	35% (22-51)	52% (34-69)
Excluding both the delayed diary and questionnaire completers						
4-week recall; last 4 weeks of diary (N=29*18)	2	16	500	4	33% (4-78)	11% (1-35)
3-month recall; full 3-month diary (N=26*18)	15	15	409	29	34% (20-50)	50% (31-69)

[a] Patients who returned the diary after >14 days. The diary was returned within 2 to 121 days (median: 8, interquartile range: 5-11) from the last date reported in the 3-month diary, which was not significantly different between the two recall groups (P=0.09).

[b] Patients who completed the questionnaire after >14 days. The questionnaire was completed within 0 to 42 days (median: 1, interquartile range: 0-4) after sending, which was not significantly different between the two recall groups (P=0.65). TP = True positive; FP = False positive; TN = True negative; FN = False negative; Se = Sensitivity; PPV = Positive Predictive Value; CI = Confidence interval.

Appendix 5. Supplemental tables chapter 4

Supplemental table 1. Comparison of possible adverse drug events (ADEs) related to blood pressure-lowering or glucose-lowering treatment between patients with or without potential overtreatment

	Blood pressure lowering treatment – possible ADEs[1]	
	Patients not overtreated	Patients with overtreatment
Y_m1, N (%)	413 (3.7)	15 (3.9)
Y, N (%)	518 (4.1)	19 (4.6)
Y_p1, N (%)	663 (4.7)	29 (6.1)
Y_p2, N (%)	540 (4.8)	**37 (8.4)*****
Y_p3, N (%)	304 (6.9)	**19 (11.7)***
	Glucose lowering treatment – possible ADEs[2]	
	Patients not overtreated	Patients with overtreatment
Y_m1, N (%)	363 (3.1)	**17 (5.7)****
Y, N (%)	521 (3.9)	15 (4.8)
Y_p1, N (%)	607 (4.1)	16 (4.7)
Y_p2, N (%)	670 (5.8)	**23 (9.6)***
Y_p3, N (%)	432 (9.8)	11 (10.7)

[1] ADEs included for blood pressure-lowering treatment were hypotension, dizziness, headache as well as unspecified coded ADEs (ICPC code A85 or WCIA code 1830) assigned to blood pressure-lowering drugs in the electronic medical record during the corresponding year.

[2] ADEs included for glucose-lowering treatment were hypoglycaemia as well as unspecified coded ADEs (ICPC code A85 or WCIA code 1830) assigned to glucose-lowering drugs in the electronic medical record during the corresponding year.

* P <0.05; ** P<0.01; *** P=0.001.

Supplemental table 2. Sensitivity analyses using more relaxed definitions of overtreatment.

	Baseline	Entry DM-program	Follow-up year 1	Follow-up year 2	Follow-up year 3
Blood pressure-lowering treatment					
With SBP measurement (% of all patients)	11,522 (84.4)	12,929 (86.9)	14,580 (89.8)	11,706 (91.2)	4,575 (94.1)
N SBP <120 mmHg	888	934	977	872	343
N SBP <120 mmHg with potential overtreatment (% of eligible patients)	115 (13.0)	126 (13.5)	141 (14.4)	127 (14.6)	54 (15.7)
N classes >= 3†	100 (11.3)	113 (12.1)	124 (12.7)	116 (13.3)	46 (13.4)
N intensified†	21 (2.4)	24 (2.6)	25 (2.6)	16 (1.8)	13 (3.8)
Glucose-lowering treatment					
With HbA_{1c} measurement (% of all patients)	12,121 (88.8)	13,549 (91.1)	15,002 (92.4)	11,886 (92.6)	4,503 (92.6)
N HbA_{1c} <6% (42 mmol/mol)	1,300	1,208	1,267	984	349
N HbA_{1c} <6% (42 mmol/mol) with potential overtreatment (% of eligible patients)	77 (5.9)	71 (5.9)	72 (5.7)	52 (5.3)	32 (9.2)
N classes>=3†	11 (0.8)	5 (0.4)	5 (0.4)	2 (0.2)	1 (0.3)
N insulin use†	47 (3.6)	39 (3.2)	45 (3.6)	38 (3.9)	22 (6.3)
N intensified†	20 (1.5)	28 (2.3)	24 (1.9)	12 (1.2)	11 (3.2)

Baseline = Year before entry to the disease management program; Entry DM-program = Entry to disease management program; Follow-up year 1 = 1 year after entry; Follow-up year 2 = 2 years after entry; Follow-up year 3 = 3 years after entry; SBP = Systolic blood pressure; HbA_{1c} = glycohemoglobin.
† Percentages do not sum to the percentages of patients with potential overtreatment because patients can be included in multiple categories of overtreatment.

Supplemental table 3. General practices with a ≥5% increase, ≥5% decrease or stable percentage of under- and overtreated patients to systolic blood pressure (SBP) or glycohemoglobin (HbA_{1c}) at one year after entry to the disease management program compared to baseline

	SBP overtreatment (% within SBP undertreatment)[1]				
	Decrease	Stable	Increase	Row total (% of total)	P-value*
SBP undertreatment					0.02
Decrease	26 (45.6)	11 (19.3)	20 (35.1)	57 (43.5)	
Stable	15 (36.6)	20 (48.8)	6 (14.6)	41 (31.3)	
Increase	13 (39.4)	8 (24.2)	12 (36.4)	33 (25.2)	
Row total (% of total)	54 (41.2)	39 (29.8)	38 (29.0)		
	HbA_{1c} overtreatment (% within HbA_{1c} undertreatment)				
	Decrease	Stable	Increase	Row total (% of total)	P-value*
HbA_{1c} undertreatment					0.13
Decrease	3 (9.1)	17 (51.5)	13 (39.4)	33 (24.8)	
Stable	10 (27.0)	19 (51.4)	8 (21.6)	37 (27.8)	
Increase	14 (22.2)	37 (58.7)	12 (19.0)	63 (47.4)	
Row total (% of total)	27 (20.3)	73 (54.9)	33 (24.8)		

* χ^2-test; [1] Numbers do not sum to 133 GPs because two GPs were excluded due to no denominator (no patients with an SBP <130mmHg).

Appendix 6. Supplemental tables chapter 5

Supplemental table 1. Association between self-reported life-expectancy and age[†]

		Self-reported life-expectancy*[‡]			
		≤2 years	>2 and ≤5 years	>5 and ≤10 years	>10 years
Age	<65 years	0 (0%)	0 (0%)	2 (4%)	45 (96%)
	≥65 and <75 years	0 (0%)	1 (2%)	12 (24%)	36 (73%)
	≥75 and <85 years	2 (8%)	12 (48%)	6 (24%)	5 (20%)
	≥85 years	0 (0%)	3 (75%)	0 (0%)	1 (25%)

* N = 126 since 26 patients did not report their life-expectancy

[‡] The age of how old patients expect they will become ranged from 70 to 100 for both males and females. Most patients reported to become 80 years (30% of the males, 37% of the females)

[†] Fisher freeman-halton test revealed a P-value of <0.001

Supplemental table 2. Preferences of patients aged <75 years and ≥75 years including patients who failed the dominant choice set

Constant and attributes	<75 years[a]		≥75 years[b]	
	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value
Constant (additional drug)	-0.79 (-1.31 – -0.26)	**0.003**	-1.19 (-1.98 – -0.39)	**0.003**
Blood pressure	-0.09 (-0.10 – -0.07)	**0.000**	-0.05 (-0.07 – -0.03)	**0.000**
Death within the next 5 years	-20.67 (-28.18 – -13.16)	**0.000**	-21.58 (-33.22 – -9.94)	**0.000**
Limitations heart attack	-6.24 (-21.15 – 8.66)	0.412	-8.55 (-31.67 – 14.57)	0.469
Limitations stroke	-25.55 (-40.55 – -10.56)	**0.001**	-10.12 (-33.26 – 13.03)	0.392
Adverse drug events	-15.22 (-18.36 – -12.07)	**0.000**	-9.52 (-14.22 – -4.82)	**0.000**
Additional tablet in the evening	0.13 (-0.07 – 0.33)	0.193	0.04 (-0.26 – 0.35)	0.778
Combination tablet	0.13 (-0.08 – 0.33)	0.224	0.16 (-0.14 – 0.46)	0.302

[a] Number of observations 3,330 (111 patients * 10 choice sets * 3 alternatives per choice set)

[b] Number of observations 1,500 (50 patients * 10 choice sets * 3 alternatives per choice set)

Supplemental table 3. Preferences of patients aged <65 years and ≥80 years

Constant and attributes	<65 years[a]		≥80 years[b]	
	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value
Constant (additional drug)	-0.09 (-0.83 – 0.65)	0.813	-0.24 (-1.82 – 1.34)	0.765
Blood pressure	-0.07 (-0.09 – -0.04)	**0.000**	-0.06 (-0.11 – -0.01)	**0.017**
Death within the next 5 years	-22.41 (-33.25 – -11.58)	**0.000**	-15.81 (-40.24 – 8.62)	0.205
Limitations heart attack	-10.76 (-32.07 – 10.55)	0.323	29.90 (-18.91 – 78.72)	0.230
Limitations stroke	-27.92 (-49.29 – -6.54)	**0.010**	-20.15 (-69.44 – 29.15)	0.423
Adverse drug events	-18.42 (-22.99 – -13.86)	**0.000**	-21.60 (-32.02 – -11.19)	**0.000**
Additional tablet in the evening	0.09 (-0.19 – 0.38)	0.532	-0.40 (-1.05 – 0.24)	0.219
Combination tablet	0.07 (-0.22 – 0.36)	0.645	0.07 (-0.54 – 0.68)	0.828

[a] Number of observations 1,560 (52 patients * 10 choice sets * 3 alternatives per choice set)
[b] Number of observations 450 (15 patients * 10 choice sets * 3 alternatives per choice set)

Appendix 7. Supplemental tables chapter 6

Supplemental table 1. Differences between patients included and excluded from analyses

	Included	Excluded	P-value
Glucose-lowering drugs			
Females (%)	38 (44.7)	28 (58.3)	0.131*
Mean age in years (SD)	65.8 (9.5)	67.1 (9.7)	0.471†
Education (%)			0.261*
Low education	41 (48.8)	29 (60.4)	
Middle education	23 (27.4)	6 (12.5)	
High education	15 (17.9)	10 (20.8)	
Other	5 (6.0)	3 (6.3)	
Mean BMI (SD)	29.0 (4.0)	29.9 (4.9)	0.252†
Median diabetes duration (IQR)	7 (5.0 – 11.0)	5 (3.0 – 9.0)	0.039‡
Blood pressure-lowering drugs			
Females (%)	34 (50.7)	32 (48.5)	0.794*
Mean age in years (SD)	65.9 (10.1)	66.6 (9.1)	0.644†
Education (%)			0.702*
Low education	32 (48.5)	38 (57.6)	
Middle education	17 (25.8)	12 (18.2)	
High education	13 (19.7)	12 (18.2)	
Other	4 (6.1)	4 (6.1)	
Mean BMI (SD)	29.7 (4.7)	29.0 (3.9)	0.367†
Median diabetes duration (IQR)	7 (5.0 – 11.0)	6 (3.0 – 10.0)	0.206‡
Lipid-lowering drugs			
Females (%)	39 (45.9)	27 (56.3)	0.251*
Mean age in years (SD)	65.7 (9.9)	67.3 (9.0)	0.373†
Education (%)			0.341*
Low education	42 (50.0)	28 (58.3)	
Middle education	22 (26.2)	7 (14.6)	
High education	14 (16.7)	11 (22.9)	
Other	6 (7.1)	2 (4.2)	
Mean BMI (SD)	29.2 (4.3)	29.6 (4.4)	0.676†
Median diabetes duration (IQR)	7 (3.0 – 10.0)	6.5 (4.0 – 10.8)	0.609‡

BMI = Body mass index; SD = Standard deviation; IQR = Interquartile range

* Pearson χ^2-test; † T-test; ‡ Mann-Whitney U test

Supplemental table 2. Patient characteristics of the adherers, unintentional non-adherers and intentional non-adherers to glucose-, blood pressure-, and lipid-lowering drugs

	Adherers	Unintentional non-adherers	Intentional non-adherers	P-value
Glucose-lowering drugs				
N	53	22	10	
Females (%)	28 (52.8)	8 (36.4)	2 (20.0)	0.105*
Mean age in years (SD)	67.2 (10.0)	64.1 (7.4)	62.3 (10.0)	0.209†
Education (%)				0.274*
Low education	31 (59.6)	7 (31.8)	3 (30.0)	
Middle education	11 (21.2)	9 (40.9)	3 (30.0)	
High education	8 (15.4)	4 (18.2)	3 (30.0)	
Other	2 (3.8)	2 (9.1)	1 (10.0)	
Mean BMI (SD)	29.1 (4.2)	27.7 (3.2)	31.6 (3.2)	0.033† [1]
Median diabetes duration (IQR)	7 (3.0-10.0)	8 (6.0-12.5)	7 (5.5-14.5)	0.196‡
Measurement outside GPs office				0.012*[2]
Yes (%)	8 (16.0)	9 (40.9)	5 (55.6)	
Blood pressure-lowering drugs				
N	53	10	4	
Females (%)	26 (49.1)	5 (50.0)	3 (75.0)	0.605*
Mean age in years (SD)	66.1 (0.9)	67.9 (10.1)	58.3 (16.5)	0.259†
Education (%)				0.147*
Low education	29 (55.8)	2 (20.0)	1 (25.0)	
Middle education	12 (23.1)	4 (40.0)	1 (25.0)	
High education	9 (17.3)	2 (20.0)	2 (50.0)	
Other	2 (3.8)	2 (20.0)	0 (0.0)	
Mean BMI (SD)	30.1 (0.5)	27.6 (2.7)	28.9 (6.3)	0.290†
Median diabetes duration (IQR)	7 (5.0-9.0)	12 (6.8-14.5)	4.5 (2.5-6.5)	0.030‡[3]
Measurement outside GPs office				0.078*
Yes (%)	13 (24.5)	2 (20.0)	3 (75.0)	
Lipid-lowering drugs				
N	67	15	3	
Females (%)	31 (46.3)	7 (46.7)	1 (33.3)	0.906*
Mean age in years (SD)	66.4 (9.1)	62.5 (9.1)	66.7 (25.8)	0.394†
Education (%)				0.084*
Low education	38 (57.6)	3 (20.0)	1 (33.3)	
Middle education	16 (24.2)	5 (33.3)	1 (33.3)	
High education	7 (10.6)	6 (40.0)	1 (33.3)	
Other	5 (7.6)	1 (6.7)	0 (0.0)	
Mean BMI (SD)	29.5 (4.5)	28.3 (3.3)	27.9 (1.7)	0.515†
Median diabetes duration (IQR)	6 (3.0-9.0)	8 (5.8-12.3)	3[a]	0.090‡
Measurement outside GPs office				0.741*
Yes (%)	6 (9.0)	2 (13.3)	0 (0.0)	

GPs = General practitioners; BMI = Body mass index; SD = Standard deviation; IQR = Interquartile range;
* Pearson χ^2-test; † One-way analysis of variance; ‡ Kruskal-Wallis test
[a] No IQR due to low numbers
[1] Significance due to difference between unintentional and intentional non-adherers (P = 0.003)
[2] Significance due to difference between adherers and intentional non-adherers (P = 0.008)
[3] Post-hoc analysis did not reveal any significant differences

Curriculum vitae

Sieta de Vries was born on July 27th, 1986 in Drachten, the Netherlands. After finishing secondary school in 2003, she started her study, Sport & Health, at the Hanze University in Groningen. In 2007, she graduated from this educational program and continued with a pre-master program Psychology at the University of Groningen. She combined this educational program with a research project at the Hanze University Sports Science Research Group, where she evaluated the Groninger Sport Model.

In 2009, she started the master program Social Psychology at the University of Groningen, and obtained her master's degree in 2010. At the department of Health Psychology of the University Medical Center Groningen (UMCG), Sieta wrote her master thesis "The reliability and validity of an implicit coping- and wellbeing-test".

From December 2010 to December 2014, she worked at the department of Clinical Pharmacy and Pharmacology of the UMCG on her PhD-project on patient perspectives in the benefit-risk evaluation of drugs. In the period 2011 – 2013, she was a member of the PhD council of the graduate school SHARE of the University of Groningen.

In December 2014, she started working as a post-doc researcher on the Innovative Medicines Initiative (IMI) Web-RADR project and the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) project at the department of Clinical Pharmacy and Pharmacology of the UMCG.

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Groningen, December 2014
Sieta de Vries

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Patient perspectives in the benefit-risk evaluation of drugs

The patient perspective in the process of drug evaluation and drug use is high on the agenda, which is demonstrated by an increased use of patient-reported outcome instruments to evaluate drugs and a shift towards patient-centred care in clinical practice. This thesis contains studies focusing on 1) the development and validation of a patient-reported outcome instrument to assess adverse drug events (ADEs), and 2) the role of patient characteristics and preferences on treatment decisions in clinical practice. The first part presents the development of a generic questionnaire to assess ADEs from the patient perspective. Although this questionnaire showed sufficient content and concurrent validity to detect ADEs at a general level, it was not sensitive enough to detect all ADEs perceived by patients. Suggestions are provided to improve the questionnaire for future use. In the second part, insight in decisions to start or intensify treatment with special attention for different patient age groups is provided. It was found that age influenced prescribing behaviour as well as the patient's willingness to add a drug. For all patients, preventing death and ADEs were important considerations when choosing an additional drug. The influence of beliefs about benefits and risks on patients' drug adherence, however, differed among types of drugs. These findings can be used to improve the assessment of ADEs from the patient perspective, to incorporate the patient perspective in treatment decisions and to develop better tailored interventions for improving drug adherence.

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